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244

FLUDARABINE-BASED NON-MYELOABLATIVE STEM CELL TRANSPLANTATION IN A PATIENT WITH SICKLE CELL DISEASE AND RENAL FAILURE: CLINICAL OUTCOME AND PHARMACOKINETIC COMPARISON TO PATIENTS WITH NORMAL RENAL FUNCTION

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End-organ damage is common in adult patients with Sickle Cell Disease (SCD), therefore an effective non-myeloablative approach to allogeneic stem cell transplantation (SCT) would be ideal. Fludarabine is a component of most non-myeloablative conditioning regimens. Since 40% of the active metabolite, 2-fluoro-ara-A (F-Ara-A), is cleared by the kidneys, use in patients with renal insufficiency or renal failure is hazardous. We report the outcome of two adult SCD patients who underwent non-myeloablative SCT from their HLA-identical matched siblings on an NHLBI-sponsored clinical trial. Patient #1 is a 21 year-old male with normal renal function and patient #2 a 27 year old with dialysis-dependent end-stage renal disease. Conditioning consisted of Total Body Irradiation 200cGy followed by Fludarabine (Pt #1: 30 mg/m^2, Pt #2: 24 mg/m^2) Cyclophosphamide 500mg/m^2, both given over four days and Campath 1-H 100mg over 5 days. Mycophenolate Mofetil 2 grams/day was given for 100 days. Patient #1 and #2 received peripheral blood stem cell grafts containing 21×10^6 and 19×10^6 CD34$^+$ cells/kg, respectively. Patient #2 underwent 6 hours of conventional hemodialysis using an F200 dialyzer, 12 hours after each Fludarabine dose. Plasma samples from patient #2 and two additional non-SCD patients with normal renal function undergoing stem cell transplantation using the same chemotherapy preparative regimen were collected over 24 hours after doses 1 and 4 of Fludarabine. F-Ara-A was measured by a validated LC/MS/MS assay. Both SCD patients achieved full donor erythroid chimerism and stable mixed lymphoid and myeloid chimerism (donor CD15/CD3; Pt #1 89%/87% 14 months post-transplant, Pt #2 86%/45% 6 months post transplant). Neither patient developed graft vs host disease, neurological complications or any other SCD-related complications following transplantation. Both have normal blood counts and are on no immunosuppressive medications. F-Ara-A pharmacokinetic parameters obtained using non-compartmental analysis are given in the table. With a 20% dose reduction followed by intensive daily dialysis, we achieved Fludarabine levels that are nearly identical to that achieved in patients with normal renal function. This allowed for robust donor stem cell engraftment without Fludarabine-related toxicity. We conclude that non-myeloablative allogeneic SCT for adult patients with SCD is feasible, even in the setting of end-stage renal disease.

First Dose Fludarabine Pharmacokinetic Parameters

Patient with:	C_{max} (μ/L)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)	AUC_{last} (mg·h/L)
Renal Failure and SCD	**549**	**5.9**	**5.3***	**52**	**4093**
Normal Renal Function-1	**788**	**10.5**	**6.4**	**72.6**	**3972**
Normal Renal Function-2	**1170**	**9.2**	**6.4**	**59.6**	**4049**

*calculated from dialysis phase slope; **C_{max}** Maximum Concentration, **$t_{1/2}$** half life, **CL** clearance, **V_{ss}** Steady State Volume of Distribution, **AUC** Area under curve

245

DONOR KILLER IG-LIKE RECEPTOR HAPLOTYPE IS ASSOCIATED WITH LOWER RELAPSE IN CHRONIC MYELOGENOUS LEUKEMIA PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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In allogeneic hematopoietic cell transplantation (HCT), donor natural killer (NK) cells can prevent leukemia relapse and prolong survival. NK alloreactivity has been shown to be influenced by the killer Ig-like receptor (KIR) repertoire of the donor and the HLA class I KIR ligand phenotype of the recipient. We sought to determine if more activating receptors in the donor KIR repertoire would influence the outcome of allogeneic transplant for hematologic malignancies. Comprising 50% of all haplotypes in the Caucasian population, KIR haplotype-A is a conserved haplotype with nearly no activating KIR. In contrast, haplotype-B comprises a variety of different haplotypes, most of which contain several activating KIR. Using data provided from the International Histocompatibility Working Group, we studied the donor KIR genotypes from 541 unrelated donor transplants and examined the impact of donor KIR haplotype on overall surivival (OS) and relapse, by segregating donor-recipient pairs into those in which the donor was homozygous for KIR haplotype A (AA) versus those in which the donor was heterozygous or homozygous for the B-haplotype. Models were adjusted for disease severity, HLA-mismatch, and patient age. There was no survival advantage to having a donor with a B haplotype compared to AA donors (HR 1.05, 95% CI 0.80-1.37, p=0.73). However, there was a significant effect of donor B haplotype on relapse, where the presence of a donor B haplotype (n=330) compared to donor AA (n=162) was associated with significantly lower hazard of relapse (HR=0.41, 95% CI 0.33-0.67, p<0.0001). The haplotype B effect on relapse was overwhelming strong in transplants for CML (n=189, HR=0.15, 95% CI 0.08-0.27, p<0.0001). There was no significant donor B-haplotype effect on relapse in AML (n=104, HR 0.80, 95% CI 0.40-1.63, p=0.54) or ALL (n=96, HR 0.76, 95% CI 0.30-1.95, p=0.57). There was no clear association between any specific activating KIR and decreased relapse, nor was there was an association between cumulative numbers of activating KIRs and decreased relapse. These results suggest that the association between haplotype B and decreased relapse in CML may be related to factors other than activating KIR present or associated with the B-haplotypes and absent in the A-haplotype. These results have implications for donor selection in patients with CML who are referred for allogeneic transplantation.

246

ALLOGENEIC BLOOD AND MARROW TRANSPLANTATION IN THALASSEMIA MAJOR CLASS 3: AN EXPERIENCE OF IRAN

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Objective: Our aim for this study was to describe the outcome of blood and marrow transplantation in patients with class 3 Thalassemia major.

Methods: Since December 1992 till september 2006, fifty-two patients with Thalassemia class 3 received blood and marrow transplantation from their Human Leukocyte Antigen(HLA)-identical siblings. Thirty-two patients received bone marrow and twenty patients received peripheral blood stem cell transplantation. Conditioning regimen in 47 patients was Cyclophosphamide 40 mg/kg/day (from day–5 to -2) and Busulfan 3.5 mg/kg/day (from day –9 to -6) and in these patients Graft Versus Host Disease (GVHD) prophylaxis regimen was Cyclosporine.A (CY.A) 1.5mg/kg /day/IV (day–3), then 3mg/kg/day IV (days +7, +11), then 12.5 mg/kg/day/PO and Methotrexate 10mg/m^2 (day +1), 6mg/m^2 (days +3, +6). Conditioning regimen in 5 patients was Fludarabin 40 mg/m^2 (from –6 to –2) and Busulfan 4 mg/kg (from –5 to –2) and in this patients GVHD prophylaxis regimen was (CY.A) 3 mg/kg/day IV (days –3 and +7), then 12.5 mg/kg/day PO.

Results: Median age at time of transplantation was 8.5 years (age range: 1-26), Male/Female: 21/31.Median time of absolute

neutrophil count $\geq 0.5\times10^9$ /L was +14 and Median time of platelet recovery $\geq 20\times10^9$ /L was +25. At present 42 out of 52 are alive and 10 patients died due to acute GVHD, chronic GVHD, rejection, veno-occlusive disease, infection and the others. Thirty-four patients (64%) developed acute GVHD (grade I = 13, grade II = 7, grade III= 10, grade IV= 4). Three patients (5.8%) developed chronic GVHD (limited= 2, extensive= 1). 8-year disease free survival were 73.17%. 8-year overall survival were 79.85%.

Conclusion: According to this study, for an acceptable outcome in Thalassemia class 3We need better conditioning and GVHD prophylaxis regimens to decrease cardiopulmonary and liver complications. The results of blood and marrow transplantation showed that it is better than supportive therapy such as transfusion and desferal therapy.

247

OUTCOME OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CHILDREN WITH ACUTE MYELOGENOUS LEUKEMIA IN SECOND COMPLETE REMISSION, SINGLE CENTRE EXPERIENCE

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Allogeneic hematopoietic stem cell transplantation (HSCT) is proven to be an effective modality of treatment for children with high risk or relapsed acute myelogenous leukemia (AML). Survival rate as high as 72% has been reported when offered to patients in first complete remission (CR1). The outcome for children transplanted in second complete remission is less favourable with reported survival ranging from 40 to 58%. We reviewed 26 consecutive pediatric patients with AML who received allogeneic HSCT in CR2 between 1994 and 2005 in the Hospital for Sick Children, Toronto, Canada. Twenty-two patients transplanted in CR2 after chemotherapy only relapse and 4 patients suffered relapse after first allogeneic transplant and received second allogeneic HSCT in CR2. Conditioning regimens included cyclophosphamide 50mg/kg infused over 1 hour daily for 4 days and fractionated total body irradiation (TBI; 1200cGy) in six fractions over 3 days (CY/TBI) in 13 patients, 2 patients received Busulfan infused every 6 hours for 4 days followed by cyclophosphamide 50mg/kg infused over 1 hour daily for 4 days (Bu/CY), 5 patients received ATG in addition to the Bu/CY regimen and 6 patients received other conditioning regimens. Median age at transplant was 8.3 years (range 2.2-18.2 years). Four patients received matched sibling donor (MSD), 5 patients received one antigen mismatched related donor (MMRD), 16 patients received unrelated donors and 1 patient received unrelated cord progenitor stem cells. Primary graft failure was encountered in 2 patients, 1 patient was re-transplanted successfully and remains alive in remission and the other patient died of sepsis and respiratory failure. The rest of the patients engrafted at a median of 20 days (range 10-35 days). Acute grade III-IV and chronic GVHD occurred in 9 patients (35%). Six patients (23%) suffered relapse, 4 of them died and two are still alive at 2495 days and 2944 days with donor leukocyte infusion (DLI) and second transplantation, respectively. Six patients (23.0%) died from TRM. Including the 2 relapsed patients who were salvaged by DLI and a second transplantation, survival was 62% with a median follow-up of 1198 days (range 53-4014 days). **Conclusion:** Survival for children transplanted in CR2 for AML is higher than previously reported, but relapse and treatment-related mortality remains a concern.

248

NOVEL TYROSINE KINASE INHIBITOR THERAPY (NTKI) PRIOR TO ALLOGENEIC STEM CELL TRANSPLANTATION (ASCT) IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA (CML): NO EVIDENCE FOR INCREASED TRANSPLANT-RELATED TOXICITY

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Introduction: Patients undergoing ASCT for CML are increasingly likely to have received a NTKI after failing imatinib mesylate. It is unknown whether the use of these NTKIs prior to ASCT increases transplant-related toxicity.

Methods: We retrospectively analyzed the outcome of 12 patients with CML (1 chronic phase, 6 accelerated phase, and 5 in blastic phase) who received dasatinib (n=2), nilotinib (n=7), or both (n=3) prior to ASCT.

Results: Median age was 41 years (range, 18-59 years). The median time on treatment was 134 days (range, 30-285 days), and the median time from the end of NTKI therapy to ASCT was 34 days (range, 7-130 days). Preparative regimen was ablative in 8 patients and non-ablative in 4. Source of stem cells were matched related donors in 7 patients, matched unrelated in 3, haplo-identical in 1, and unrelated cord blood in 1. All patients engrafted within 13 days. There was no significant early transplant-related toxicity: gastro-intestinal toxicities of grade 3 were encountered in 2 patients. One patient had secondary graft failure after 6 months from the first ASCT that required a second ASCT. Acute graft versus host disease (GVHD) of grade 2 was observed in 7 patients (58%), chronic GVHD in 6 (50%). Nine patients achieved a molecular response: four complete and five major (Q-PCR< 0.05%). Three patients had disease progression by day 30 post ASCT. Two patients have relapsed after a median of 12 months (range, 6-18 months). After a median follow-up of 10 months (range, 3-22 months), 7 patients are alive in molecular response and 5 patients died, 4 of disease progression and one of extensive chronic GVHD.

Conclusion: Previous treatment with NTKI did not increase transplant-related toxicity in this preliminary experience. Further follow-up and larger number of patients will be necessary to confirm these observations.

249

A MIND AND PHYSICAL FITNESS PROGRAM IN CANCER CARE – *FEASIBILITY OF A MULTIMODAL EXERCISE AND PSYCHO-EDUCATIONAL INTERVENTION FOR PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION. A RANDOMIZED CONTROLLED PILOT STUDY*

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Background: A pilot study incorporating a multimodal fitness and psycho-educational program to patients undergoing allogeneic stem cell transplant (allo-HSCT). The main focus of the study is to evaluate the feasibility, safety and effectiveness of a 4-6 week intervention consisting of a fitness program with progressive stationary bicycle-, muscle strength-, flexibility- and relaxation training and a cognitive based supportive and educational intervention. The aim of the study was to prevent or minimize loss of physical capacity and improve overall well being during hospitalization.

Patients and methods: 20 adult patients (18 -65 years) were randomized to either an intervention or control group using the clinical international trial management system.Through triangulation of qualitative and quantitative methods, patients are interviewed, tested for physical capacity (VO2 max, muscle strength and physical functioning), quality of life (EORTC, HADS, Fact-An and Mini-mac) prior to admission and upon discharge. Patients kept training journals and registered side effects during hospitalization. This study reports only the findings from the physical capacity tests.

Results and Conclusion

Of the 22 eligible patients who met the eligibility criteria, 20 agreed to participate (90.9%).14 of 20 patients (70%) completed all study requirements. In the intervention group, 6 of 9 patients completed all study requirements (66.7% retention rate). Adherence to the intervention showed that patients trained 94% of the total expected training days. No adverse reactions or events that can be attributed to either the testing or exercise program were reported or observed. Pre test scores showed similiar values in both groups for all physical capacity tests. Upon